READER 4

SPEAKER: MICHAEL KANG

MARCH 3, 2014

STEM CELL AGING

RECOMMENDED READING

***You are encouraged to read these, but you will not be quizzed on them.**

The Genetics of Ageing

http://www.nature.com/nature/journal/v464/n7288/full/nature08980.html

How Stem Cells Age and Why This Makes Us Grow Old

http://www.ncbi.nlm.nih.gov/pubmed/17717515

MUSCLE AGING LINKED TO STEM CELL OVERDRIVE

Sep 28, 2012

A protein that drives the generation of new muscle fibers from stem cells during development and after injury paradoxically also appears to be responsible for the gradual decline in our muscles' ability to repair as we age. In vitro and in vivo studies by scientists at Massachusetts General Hospital (MGH), Kings College London, and Harvard Stem Cell Institute have found that the protein, fibroblast growth factor-2 (fgf2), is naturally overexpressed in aging muscles, and effectively sends muscle stem cells into overdrive, preventing them from replenishing their own populations and reducing their ability to keep muscles in tiptop condition.

A rare population of muscle stem cells—also called satellite cells—is found in every skeletal muscle. The cells reside in a dormant, or quiescent state, but can be mobilized rapidly to differentiate into new muscle cells following injury, and also generate a replacement pool of stem cells that revert back to a healthy dormant state until next required.

Initial studies in mice by scientists at MGH showed that the numbers of these dormant satellite cells in muscle decline with age, and the cells also lose markers of quiescence and self-renewal and gain markers of differentiation and apoptosis. In their hunt for factors expressed in the muscle fiber that might trigger this change in satellite cells, they found that fgf2—which is one of the natural triggers for stem cell mobilization and differentiation—are markedly elevated in the niche, or microenvironment, that surrounds stem cells in aging muscle.

Critically, in vitro and in vivo mouse studies demonstrated that the high levels of fgf2 in aged muscle effectively kicks the stem cells out of their quiescent state and triggers them to proliferate and differentiate, preventing the replenishment of the pool of quiescent stem cells, and effectively leading to a depleted satellite cell population and thus reduced ability of muscle to regenerate.

Andrew S. Brack, M.D., and colleagues also showed that either blocking fgf2 signaling or chemically inhibiting fgf2 using tamoxifen significantly increased the numbers of satellite cells in aged muscle, and boosted the ability of muscles in old mice to undergo self-repair and regenerate after injury. "To our knowledge, this is the first identification of a ligand that specifically increases within a mammalian aged niche that can promote breaks in quiescence leading to declines in stem cell function and number during homeostasis," they write in their published paper in Nature, which is titled "The aged niche disrupts muscle stem cell quiescence."

Dr. Brack puts the results into the context of an athlete's training schedule. "Analogous to the importance of recovery for athletes training for a sporting event, we now know that it is essential for adult stem cells to rest between bouts of expenditure. Preventing stem cell recuperation leads to their eventual demise...That makes sense to us as humans, in terms of the need to sleep and to eat a healthy diet, but that the need to rest also plays out at the level of stem cells is quite remarkable."

What isn't yet known is why levels of fgf2 are naturally increased in aged muscle. The MGH and Kings' College investigators suggest it may be a cell-autonomous response that is trying to keep aging muscle in

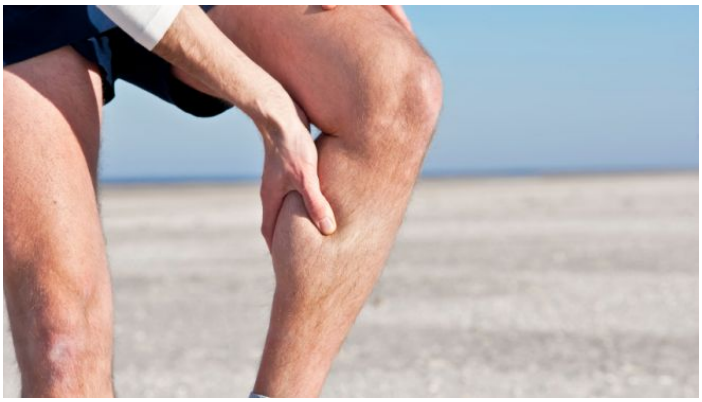
good condition. Their findings in mice also need to be validated in humans to see if the same mechanism is responsible for stem cell depletion in human muscle fibers, and age-related loss of muscle mass and muscle wastage.

Even so, states co-author Albert Basson, M.D., at Kings College, the findings open up the possibility that it may one day be possible to develop treatments to rejuvenate old, tired muscles. "If we could do this, we may be able to enable people to live more mobile, independent lives as they age...Preventing or reversing muscle wasting in old age in humans is still a way off, but this study has for the first time revealed a process that could be responsible for age-related muscle wasting."

http://www.genengnews.com/gen-news-highlights/muscle-aging-linked-to-stem-cell-overdrive/81247399/

REVERSE AGING? SCIENTISTS FIND WAY TO MAKE OLD MUSCLES YOUNG AGAIN

September 27, 2012



It is a dream for everyone as they grow older to turn back the clock and live in a younger body once again. While many have developed ways to make the body look younger cosmetically, there have been very few effective methods to combat the aging process within the body – until now.

For the first time ever, researchers have identified a crucial protein responsible for the decline of muscle repair and agility as the body ages. Upon this discovery, the scientists were able to effectively halt muscle decline in mice, giving hope to similar treatments for humans in the future.

According to the study's authors, loss of muscle strength and repair is one of the major concerns facing elderly citizens.

"A great advantage of medicine is that people are not dying as early as they used to, but the body hasn't figured out how to maintain its muscle repair," Andrew Brack, of the Massachusetts General Hospital Center for Regenerative Medicine and corresponding study author, told FoxNews.com. "The average loss of muscle mass for the 80-year-old male is 40 percent. Elderly people will fall over and break bones, they go to the hospital where they lose more muscle strength, and then don't recover."

Brack noted that muscle strength is also one of the main factors that keeps elderly individuals out of the hospital and allows them to be productive members of the workforce. In order to combat this muscle decline, Brack and Albert Basson, who met at King's College London, teamed up to see if they could put the process in reverse.

The key revolves around stem cells found within muscles. During exercise or injury, these stem cells become activated and work fervently by dividing and multiplying into new muscle fibers that help to repair the muscle. When they are no longer need, they retreat into a reservoir within the muscle and lay dormant until they are needed again.

The problem with aging muscles is that these 'fixer' stem cells don't remain dormant when they're not needed. Instead, they become activated more and more and unnecessarily divide and multiply – causing them to die at a faster rate. Since muscles only have a finite amount of these stem cells, the quicker the cells die, the less effective muscles become at repairing themselves.

Wondering exactly why the stem cells became more activated with age, Brack and Basson screened older muscles, finding higher levels of a protein called FGF2 – a protein that stimulates cell division. The scientists figured these levels could explain the unnecessary cell activation.

"As your muscle gets old, you start making more of this FGF2 protein," Basson, senior lecturer at King's

College London Dental Institute, told FoxNews.com. "…When there's more, the FGF2 starts waking up these stem cells and they start dividing. The stem cells have a limited number of times they can divide before they die or differentiate into other cells."

Basson figured that if they were able to boost a gene called SPRY2, which inhibits FGF2, then the stem cells would lay dormant until they were absolutely needed. To test this theory, the researchers administered a common drug containing SPRY2 to suppress FGF2 levels in elderly mice. Sure enough, the drugs halted the decline of muscle stem cells in the mice.

"We think of this as the first study where we've identified something that goes wrong in the aging muscle," Basson said. "There are a number of these FGF inhibitor drugs used in clinics for cancer, so they certainly can be given to patients. But we're still quite a ways off before we can think about using this drug."

One major issue about suppressing FGF2 is that the protein is still necessary for activating stem cells when muscles encounter injury. Because of this interesting paradox, Brack imagined a future drug containing SPRY2 that would be used during the least amount of physical exertion.

"I think the favorite expression is, 'Too much of a good thing is a bad thing,'" Brack said. "…You couldn't have someone on a drug like this forever – that would be very bad. It would work in a timed-release manner – keeping FGF2 low in low demanding situations. As we go through our daily lives as aged individuals, keep FGF low, but as we workout we want FGF to go up."

With such encouraging results, coupled with the fact that FGF suppressant drugs are already on the market, Brack and Basson are eager to translate this idea into human therapies. However, Brack cautioned not to view this as a way to increase lifespan, but more of a way to enhance living as we age.

"We don't think in terms of longevity," Brack said. "Instead we want to know: how do we make it possible for an 80-year-old individual to run a marathon? The purpose is not to live to 120, but to see how healthy and vital you can be. That's the future of regenerative medicine."

Loren Grush
http://www.foxnews.com/health/2012/09/27/reverse-aging-scientists-find-way-to-make-old-muscles-young-again/#ixzz2LrRI1Czo

SHOT OF YOUNG STEM CELLS MAKES RAPIDLY AGING MICE LIVE MUCH LONGER AND HEALTHIER

Jan 4, 2012

Mice bred to age too quickly seemed to have sipped from the fountain of youth after scientists at the University of Pittsburgh School of Medicine injected them with stem cell-like progenitor cells derived from the muscle of young, healthy animals. Instead of becoming infirm and dying early as untreated mice did, animals that got the stem/progenitor cells improved their health and lived two to three times longer than expected, according to findings published in the Jan. 3 edition of Nature Communications.

Previous research has revealed stem cell dysfunction, such as poor replication and differentiation, in a variety of tissues in old age, but it's not been clear whether that loss of function contributed to the aging process or was a result of it, explained senior investigators Johnny Huard, Ph.D., and Laura Niedernhofer, M.D., Ph.D. Dr. Huard is professor in the Departments of Orthopaedic Surgery and of Microbiology and Molecular Genetics, Pitt School of Medicine, and director of the Stem Cell Research Center at Pitt and Children's Hospital of PIttsburgh of UPMC. Dr. Niedernhofer is associate professor in Pitt's Department of Microbiology and Molecular Genetics and the University of Pittsburgh Cancer Institute (UPCI).

"Our experiments showed that mice that have progeria, a disorder of premature aging, were healthier and lived longer after an injection of stem cells from young, healthy animals," Dr. Niedernhofer said. "That tells us that stem cell dysfunction is a cause of the changes we see with aging."

Their team examined a stem/progenitor cell population derived from the muscle of progeria mice and found that compared to those from normal rodents, the cells were fewer in number, did not replicate as often, didn't differentiate as readily into specialized cells and were impaired in their ability to regenerate damaged muscle. The same defects were discovered in the stem/progenitor cells isolated from very old mice.

"We wanted to see if we could rescue these rapidly aging animals, so we injected stem/progenitor cells from young, healthy mice into the abdomens of 17-day-old progeria mice," Dr. Huard said.

"Typically the progeria mice die at around 21 to 28 days of age, but the treated animals lived far longer -- some even lived beyond 66 days. They also were in better general health."

As the progeria mice age, they lose muscle mass in their hind limbs, hunch over, tremble, and move slowly and awkwardly. Affected mice that got a shot of stem cells just before showing the first signs of aging were more like normal mice, and they grew almost as large. Closer examination showed new blood vessel growth in the brain and muscle, even though the stem/progenitor cells weren't detected in those tissues.

In fact, the cells didn't migrate to any particular tissue after injection into the abdomen.

"This leads us to think that healthy cells secrete factors to create an environment that help correct the dysfunction present in the native stem cell population and aged tissue," Dr. Niedernhofer said. "In a culture dish experiment, we put young stem cells close to, but not touching, progeria stem cells, and the unhealthy cells functionally improved."

Animals that age normally were not treated with stem/progenitor cells, but the provocative findings urge further research, she added. They hint that it might be possible one day to forestall the biological declines associated with aging by delivering a shot of youthful vigor, particularly if specific rejuvenating proteins or molecules produced by the stem cells could be identified and isolated.

Co-authors from the University of Pittsburgh include Mitra Lavasani, Ph.D., Aiping Lu, M.D., and Minjung Song, Ph.D., all of the Stem Cell Research Center and the Department of Orthopaedics; Andria Robinson, of UPCI and Pitt's Graduate School of Public Health; Joseph M. Feduska and Bahar Ahani of the Stem Cell Research Center; Jeremy S. Tilstra, Ph.D., and Chelsea H. Feldman of Pitt's Department of Microbiology and Molecular Genetics; and Paul D. Robbins, Ph.D., of the departments of Orthopaedic Surgery and Microbiology and Molecular Genetics, and UPCI.

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http://www.sciencedaily.com/releases/2012/01/120103135131.htm